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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/480,544	01/10/2000	JOHN H. KENTEN	0039096-0030	4434

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/480,544	KENTEN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. In view of the appeal brief filed on January 23, 2004, PROSECUTION IS HEREBY REOPENED. New rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-43 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-43 are indefinite over the recitation of "the reaction mixture" because this phrase lacks proper antecedent basis (see claims 32 and 38 step (b)). While the claims previously refer to a composition, the claims do not previously refer to a reaction mixture.

Claims 32-43 are indefinite. The claims are drawn to a method for the detection of a specific nucleic acid. However, the claims recite a final step of detecting a solid

phase-bound complex by "using said electrochemiluminescent species." The claims do not clarify the relationship between detecting the solid-phase bound complex and the detection of a specific nucleic acid. Thereby, it is unclear as to whether the claims are intended to be limited to methods for detecting a specific nucleic acid or methods for detecting a solid phase-bound complex. Additionally, the claims do not clarify what is intended to be meant by the phrase "using said electrochemiluminescent species." It is unclear as to how the electrochemiluminescent species is to be used to detect the solid-phase bound complex.

Claims 34 and 40 are indefinite over the recitation of "the binding species/binding partner pair" because this phrase lacks proper antecedent basis. While the claims previously refer to a binding species and a binding partner, the claims do not previously refer to a "binding species/binding partner pair."

Claim 36 is indefinite over the recitation of "RNA first template" because it is not clear as to what is intended to be meant by this phrase. The claim previously refers to an RNA template, but does not refer to a RNA first template. Thereby it is not clear as to whether the RNA template is intended to be the same as or different from the RNA first template. Similarly, claim 42 is indefinite over the recitation of "RNA first template."

Claims 38-43 are indefinite over the recitation of "the sample" because this phrase lacks proper antecedent basis since the claims do not previously refer to a sample.

Claims 38-43 are indefinite over the recitation of "wherein, optionally, ... said detection probe is omitted, and, optionally,...said capture-probe is omitted." The claims

are unclear because the claims first set forth a requirement for including a detection probe and a capture probe in the second mixture, but then later state that optionally both the detection probe and the capture probe may be omitted. Therefore, it is unclear as to whether in step (c) the second mixture contains or does not contain the detection probe and / or the capture probe. It is improper for the claims to simultaneously require presence of yet permit the omission of the detection and capture probes. Further, if both the detection and capture probes may be omitted, it is unclear as to how steps (d) and (e) are to be performed since the mixture will not contain probes that can hybridize to the amplified nucleic acids or probes with a binding species that binds to the binding partner. Additionally, it is unclear as to what is intended to be meant in (d) by the phrase "hybridization between said probes" because the claims define the probes as specifically hybridizing with the amplified nucleic acids, but the claims not define the probes as hybridizing to one another.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,048,687. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '687 are both inclusive of methods comprising performing a NASBA assay to obtain amplified nucleic acids, forming a second mixture containing amplified nucleic acids and a first ECL labeled detection probe and a second capture-probe labeled with a binding species, incubating the second mixture to allow hybridization of the probes to the amplified nucleic acids and to allow binding of the binding species to a binding partner immobilized on a solid-phase thereby forming a solid-phase bound complex, and detecting the solid-phase bound complex by detecting the ECL species. The present claims differ from the claims of '687 in that the present claims broadly recite that the detection and capture probes specifically hybridize with amplified nucleic acid sequences and the present claims include detecting the amplified nucleic acid sequences. The claims of '687 recite that the detection and capture probes hybridize with the RNA template and that the method includes forming a complex between the probes and the RNA template. However, the presently claimed method results in the synthesis of additional RNA templates identical to the original RNA template. The recitation in the present claims of "amplified nucleic acid sequences" necessarily includes the RNA template and the amplified copies of the RNA template. Thereby, the present claims also necessarily include the use of detection and capture probes which specifically hybridize with the RNA template and include detecting hybridization of said

probes to the amplified RNA templates. Secondly, the claims of '687 require the use of a bead which is coated with a binding species. The recitation in the present claims of a solid phase coated with a binding partner necessarily encompasses the specific species of a bead set forth in the claims of '687.

Claim Rejections - 35 USC § 103

3. Claims 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malek (5,130,238) in view of Kenten et al (Clinical Chemistry. 1991. 37(9): 1626-1632).

It is noted that the present claims are inclusive of methods for detecting a specific nucleic acid wherein the methods comprise amplifying nucleic acids by the method of NASBA, detecting the amplified nucleic acids via labeled primers or labeled nucleotides and immobilizing the amplified nucleic acids via binding-species labeled nucleotides or probes.

Malek (see Figure 1 and columns 8-10) teaches the method of NASBA which comprises (a) forming a reaction mixture comprising a sample, a first primer containing a promoter sequence, a second primer, a DNA-directed RNA polymerase, an RNA-directed RNA polymerase, a DNA-directed DNA polymerase, a ribonuclease which hydrolyzes RNA of an RNA-DNA hybrid, and one or more nucleotides, (b) incubating the reaction mixture to allow for the amplification of a specific nucleic acid sequence, and detecting the presence of the amplified nucleic acid sequence. Further, Malek teaches that the amplification process includes: (i) hybridizing the second primer to an RNA template, (ii) using the RNA template to synthesize a DNA template by extension of the second primer using the RNA-directed DNA polymerase to form a RNA-DNA

hybrid; (iii) using the ribonuclease to hydrolyze RNA in the resulting RNA-DNA hybrid; (iv) hybridizing the first primer to the newly formed DNA template; (v) extending the first primer using the DNA-directed DNA polymerase to form a double-stranded DNA product; and (vi) using the DNA-directed RNA polymerase to transcribe RNA from the double-stranded DNA.

Malek (column 11) teaches that detection of the amplified nucleic acids may be facilitated by using labeled primers or by incorporating labeled nucleotides into the amplification products. As stated by Malek (column 11), "a labeled precursor may be a ribonucleoside triphosphate for detecting RNA synthesis, or a deoxynucleoside triphosphate or an oligonucleotide primer for detecting DNA synthesis. The type of label may be a radioisotope or a useful chemical group, such as biotin, a chromophore, a fluorophore, or a hapten...In addition, the labeled DNA or RNA may be hybridized to a nucleic acid which contains a complementary sequence and which can be immobilized." Malek also teaches that the amplification products can be immobilized onto a solid support to facilitate their separation from the sample and to allow for their detection. Malek (column 11) states that "In another embodiment, the products of the amplification process may be bound to an immobilized support, hybridized to a nucleic acid probe containing a complementary sequence, and separated from the unhybridized nucleic acid which remains in solution. ..In addition, the products may contain certain chemical groups for example, biotin which may be incorporated into the products during the amplification process to allow binding to an immobilized protein, for example, avidin or

streptavidin. In addition, the products may be hybridized to a nucleic acid which contains a complementary sequence and which can be immobilized."

In summary, Malek teaches performing NASBA and detecting the amplified nucleic acids using either labeled primers or labeled nucleotides and teaches separating the amplification products from the reaction mixture by incorporating nucleotides labeled with biotin moieties or using capture probes labeled with biotin moieties followed by reacting the biotin moieties with a solid-support coated with avidin or streptavidin. Malek states that any detectable moiety may be used to label the nucleotides or primers. Malek does not specifically teach labeling the primers using an ECL label.

However, Kenten teaches methods for detecting amplification products wherein the methods comprise incorporating into the amplification products ECL-labeled primers. In particular, Kenten teaches use of the ECL label tris-ruthenium bipyridyl complex referred to there as Origin (page 1626). The reference also teaches the use of biotin-labeled primers and the immobilization of amplification products containing these primers to streptavidin-coated magnetic beads (see page 1628). Kenton (page 1626) states that "Our use of Origen label to detect and quantify PCR products demonstrates the ability of these labels to be used in conjunction with enzymatic DNA synthesis, thereby allowing the rapid detection of product without interference and with the normal specificity of DNA probes. These labels also offer simple, rapid, and nonisotopic alternatives for any previously described DNA probe assay." Further, Kenten (see Abstract) states that "These studies demonstrate the speed, specificity, and

effectiveness of the new ECL labels, compared with ^{32}P, for nucleic acid probe applications."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Malek so as to have used ECL-labeled primers and to have used biotin-labeled nucleotides or biotin-labeled probes to detect and immobilize, respectively, the amplification products. The ordinary artisan would have been motivated to have used biotin-labeled nucleotides or capture probes together with the streptavidin-coated magnetic beads because Malek and Kenton teaches that this immobilization procedure provides the advantage of allowing for the rapid and effective separation of the amplification products from the reaction mixture. Additionally, the ordinary artisan would have been motivated to have used labeled primers in the method of Malek because Malek specifically teaches that this would have provided the advantage of facilitating the detection of the amplification products. In particular, the ordinary artisan would have been motivated to have used ECL-labeled primers in the method of Malek in view of the advantages set forth by Kenten that the ECL labels provide a rapid and effective means for detecting nucleic acids.

RESPONSE TO ARGUMENTS:

In the Brief filed January 23, 2004, Applicants argue the benefits and unexpected results obtained using an ECL-labeled probe and a capture probe and in particular argue that the prior art does not teach that the ECL-labeled probe and capture probe can be added directly to the amplification mixture without removal of amplification

enzymes. At page 9 of the Brief, Applicants state that "while Claim 38 defines a patentably distinct group because an additional limitation elsewhere in the body of that claim allows for omission of the detection or capture probe, the same argument is nevertheless applicable to Claim 38 since it contains the same claim limitations at issue." However, claims 38-43 do not in fact contain the same claim limitations. Claims 38-43 allow for the omission of both the detection and capture probe. Thereby, Applicants arguments regarding the unexpected results achieved when adding the detection and capture probes directly to the amplification mixture containing a ribonuclease that cleaves RNA/DNA hybrids or of using 2 probes to hybridize simultaneously to and detect an RNA target do not apply to the present claims.

Further, Applicants argue that the prior art does not teach using ECL labels in the NASBA amplification protocol. However, Malek teaches that any detectable moiety can be used to label the primers used for the amplification reactions. While the examples provided by the Kenten reference are limited to PCR amplification, the teachings of this reference indicate that ECL labels can be used in other amplification and detection methods. Applicants state at page 13 of the Brief that "the differences between NASBA and PCR reactions are substantial and the skilled artisan would not reasonably expect that the successful incorporation of ECL technology with one would be a good predictor of success with the other." However, Applicants do not provide any specific arguments as to why ECL technology will not work with NASBA methods and Applicants have not provided any scientific evidence to substantiate the assertion that it is unpredictable that ECL labels could be used in other technologies such as NASBA. Given that Malek

teaches that the primers may be labeled with any moiety, including large moieties such as chromophores and fluorophores, and Kenten teaches labeling primers with ECL, in the absence of evidence to the contrary, the ordinary artisan would have had a reasonable expectation of success of using ECL-end labeled primers in the NASBA method of Malek.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Carla Myers
March 30, 2004

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